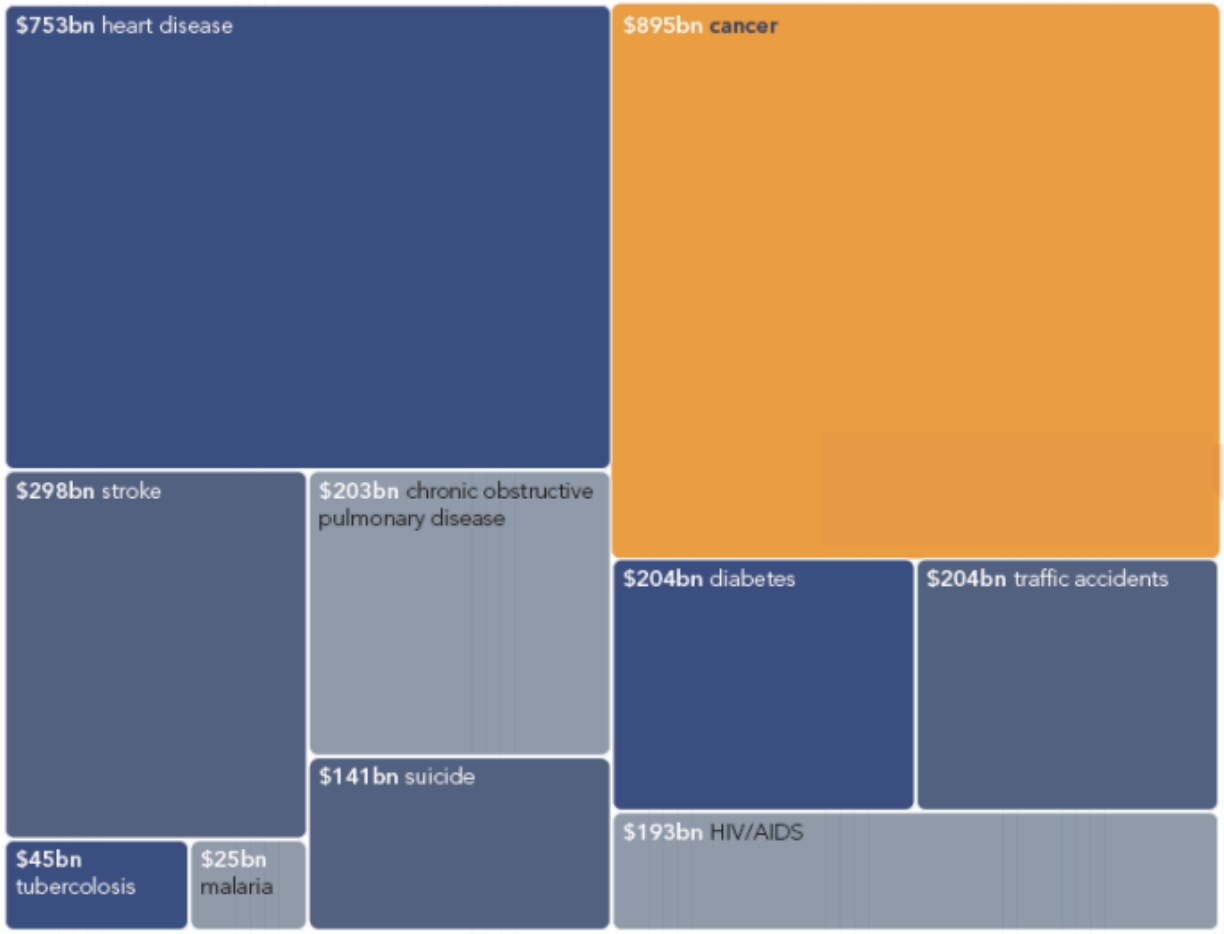
Cancer Genomes

02-710 Computational Genomics

The Economic Burden of Cancer

- The economic cost of cancer exceeds that of any other disease



The Cancer Genome Atlas

CANCER TISSUES COLLECTED FOR STUDY

Last Updated: March 04, 2016

Expand All | Collapse All

- Breast
- Central Nervous System
- Endocrine
- Gastrointestinal
- Gynecologic
- Head and Neck
- Hematologic
- Skin
- Soft Tissue
- Thoracic
- Urologic

Breast

Cancer Type	Sample Collection Complete	Data Publicly Available
Breast Ductal Carcinoma	✔	✔
Breast Lobular Carcinoma	✔	✔

Central Nervous System

Cancer Type	Sample Collection Complete	Data Publicly Available
Glioblastoma Multiforme	✔	✔
Lower Grade Glioma	✔	✔

Endocrine

Cancer Type
Adrenocortical Carcinoma
Papillary Thyroid Carcinoma
Paraganglioma & Pheochromocytoma

- Tumor gene expressions
- Tumor microRNA expression
- epigenetic data
- clinical data
- Tumor sequence data

Gastrointestinal

Overview

- What is cancer and how does it develop?
- Genetics of cancer
- Cancer subtypes and personalized medicine
- Tumor heterogeneity

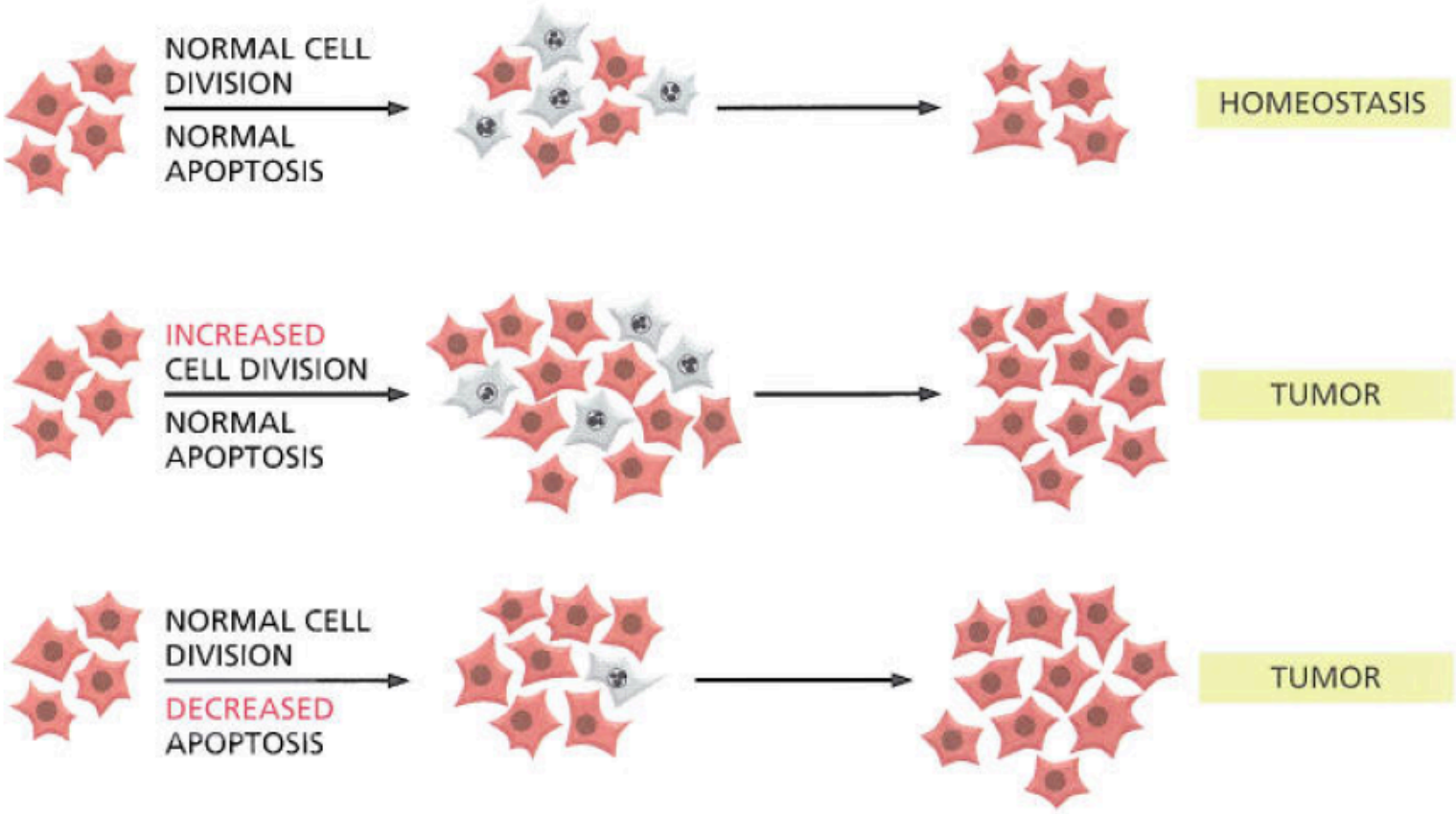
Development of Cancer Cells

- Types of cancers
  - Carcinomas: cancers arising from epithelial cells
  - Sarcomas: cancers arising from connective tissue or muscle cells
  - Leukemias and lymphomas: cancers derived from white blood cells and their precursors

- Agents that trigger carcinogenesis
  - Chemical carcinogens (causes local DNA alterations)
  - Radiation such as x-rays (causes chromosome breaks and translocations), UV light (causes DNA base alterations)
  - Viruses: Hepatitis-B, Hepatitis-C virus for liver cancer

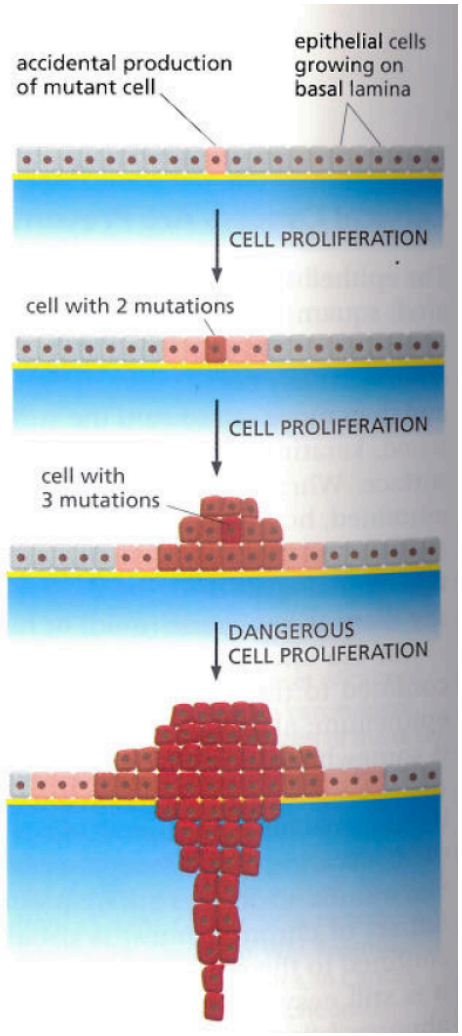
Defective Control of Cell Death and Differentiation in Cancer Cells

- Both increased cell division and decreased apoptosis (cell death) can contribute to tumorigenesis

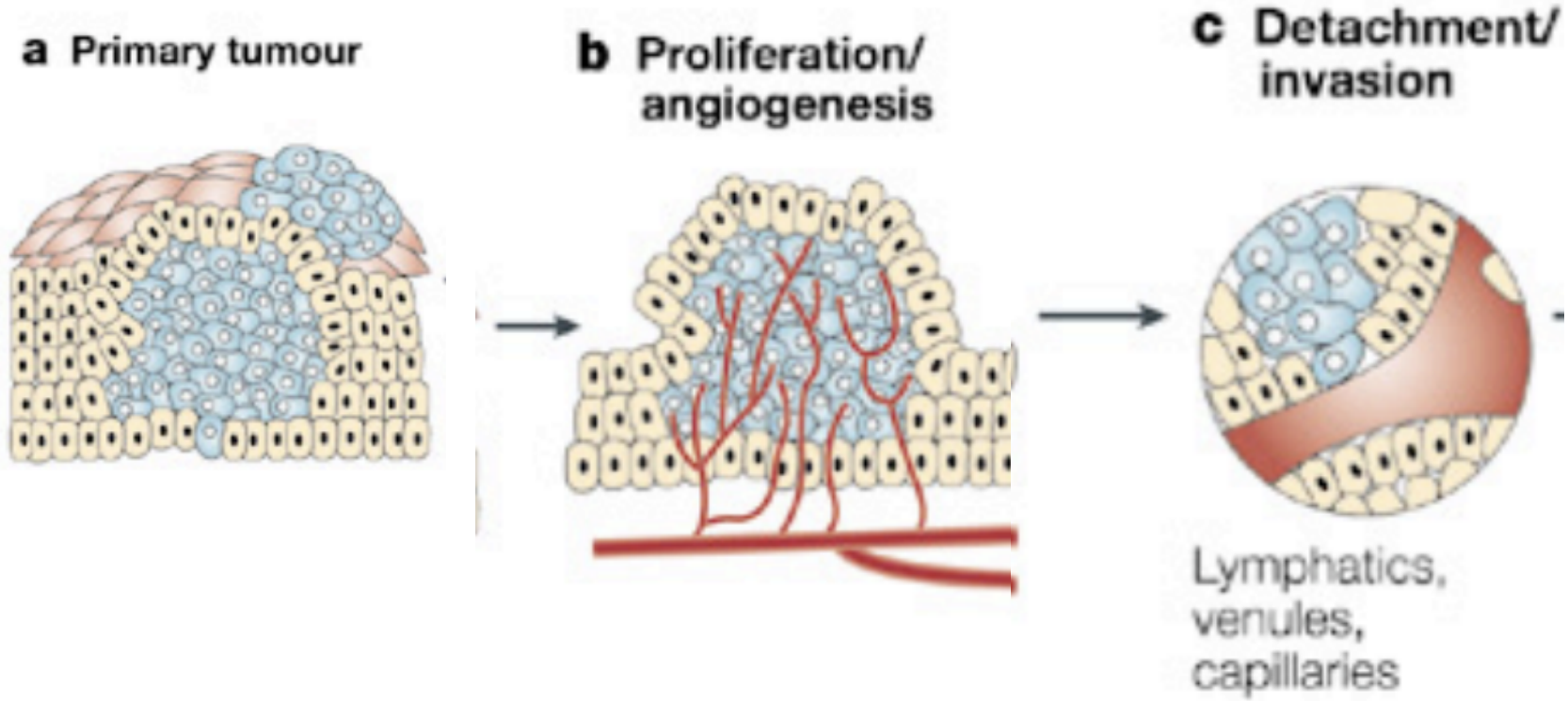


Tumors

- Cancer cells
  - Reproduce in defiance of the normal restraints on cell growth and division
  - Invade and colonize territories normally reserved for other cells



Cancer Progression



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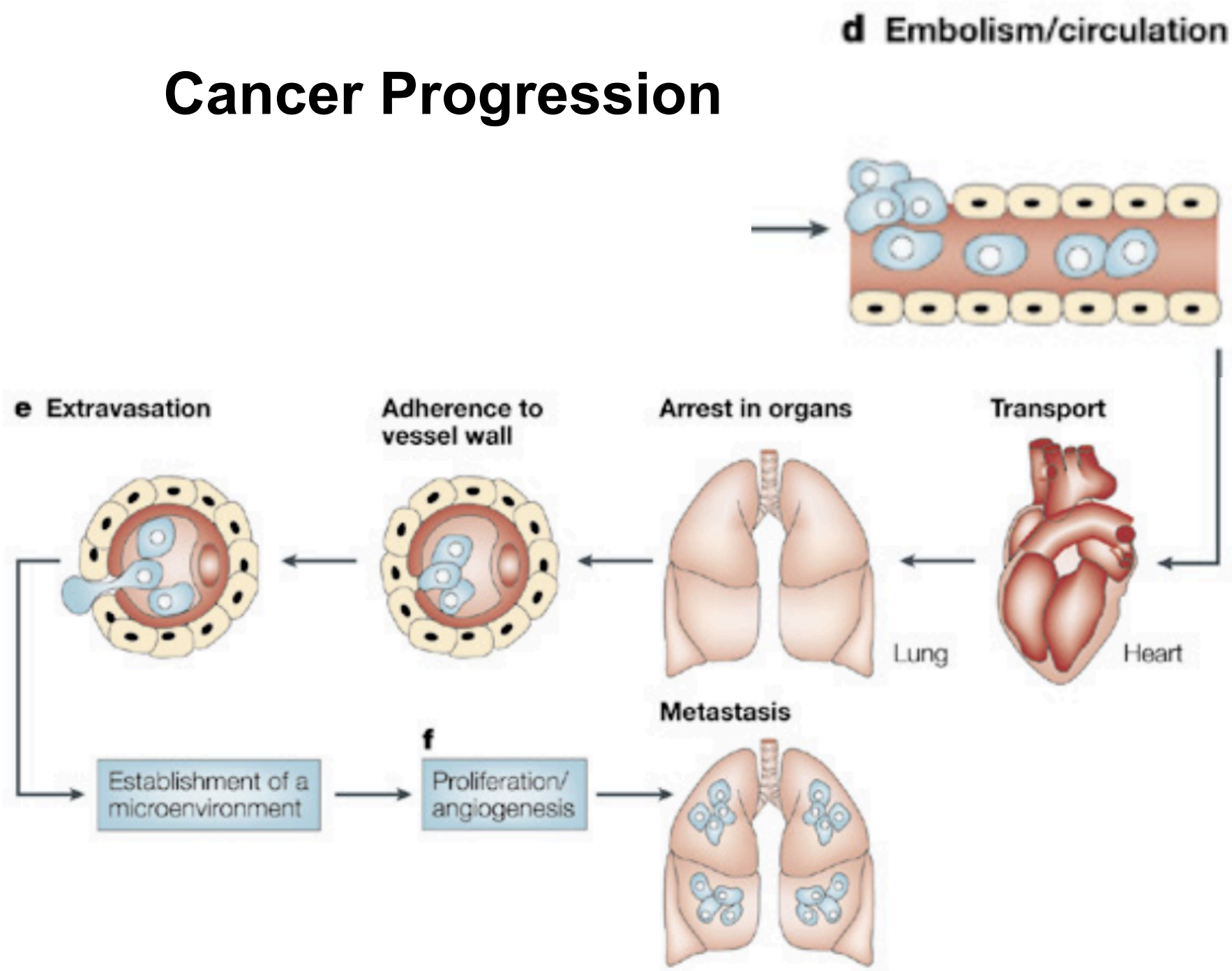

Overview

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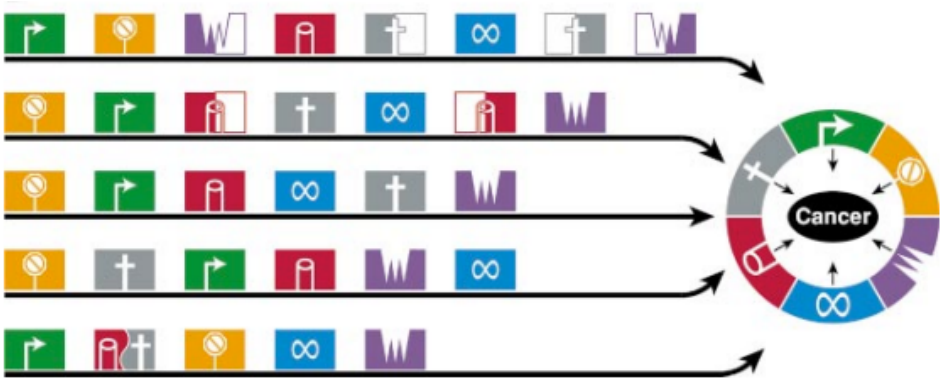
Pathways of Tumorigenesis



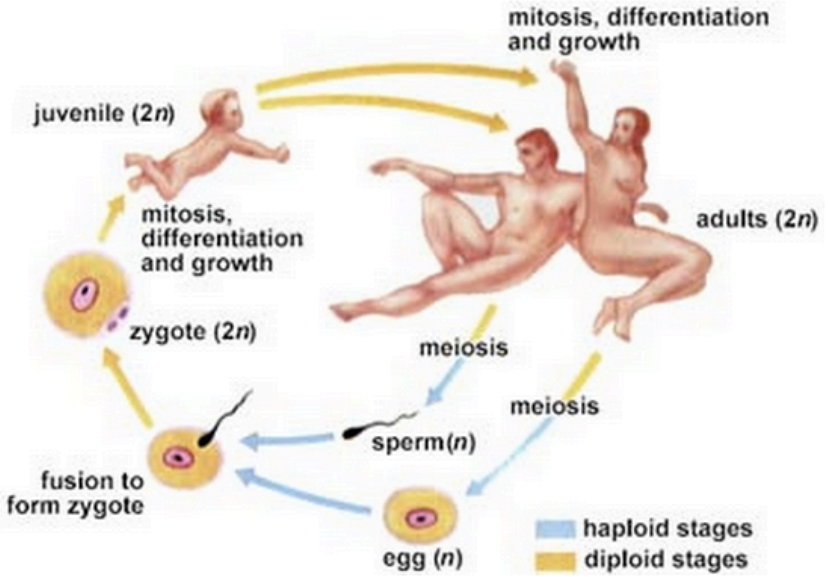
Component	Acquired Capability	Example of Mechanism
	Self-sufficiency in growth signals	Activate H-Ras oncogene
	Insensitivity to anti-growth signals	Lose retinoblastoma suppressor
	Evading apoptosis	Produce IGF survival factors
	Limitless replicative potential	Turn on telomerase
	Sustained angiogenesis	Produce VEGF inducer
	Tissue invasion & metastasis	Inactivate E-cadherin

Germline vs Somatic Mutations

- Germline mutations
  - Any detectable and heritable variation in the lineage of germ cells
  - Mutations in these cells are transmitted to offspring
  - So far, we focused on germline mutations for complex diseases

- Somatic mutations
  - Mutations in non germline cells
  - These mutations are not transmitted to offsprings

- Cancer can be caused by both germline and somatic mutations



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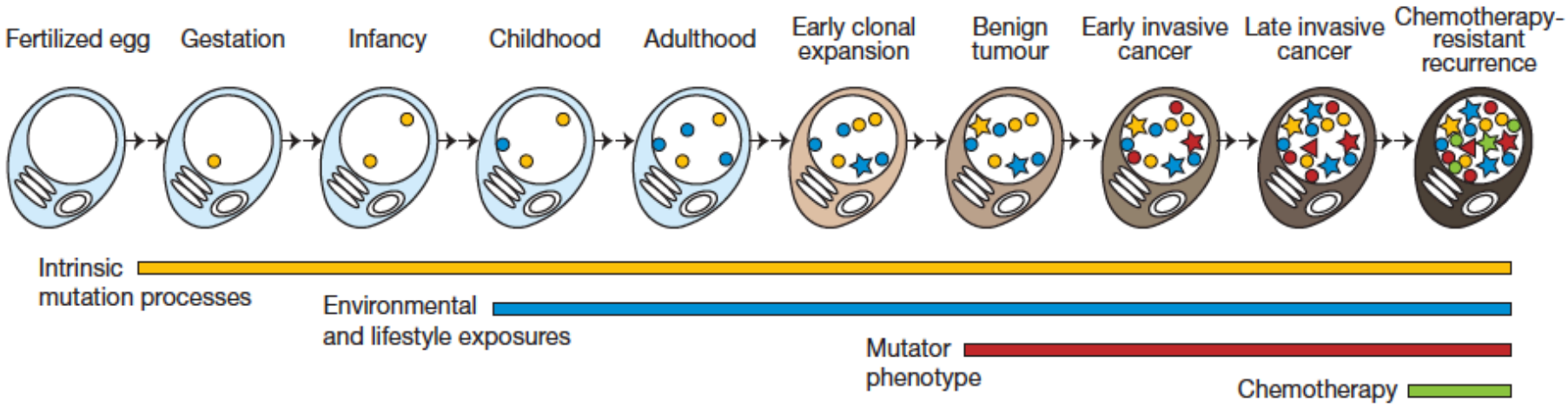


Mutations can be on genomes or epigenomes

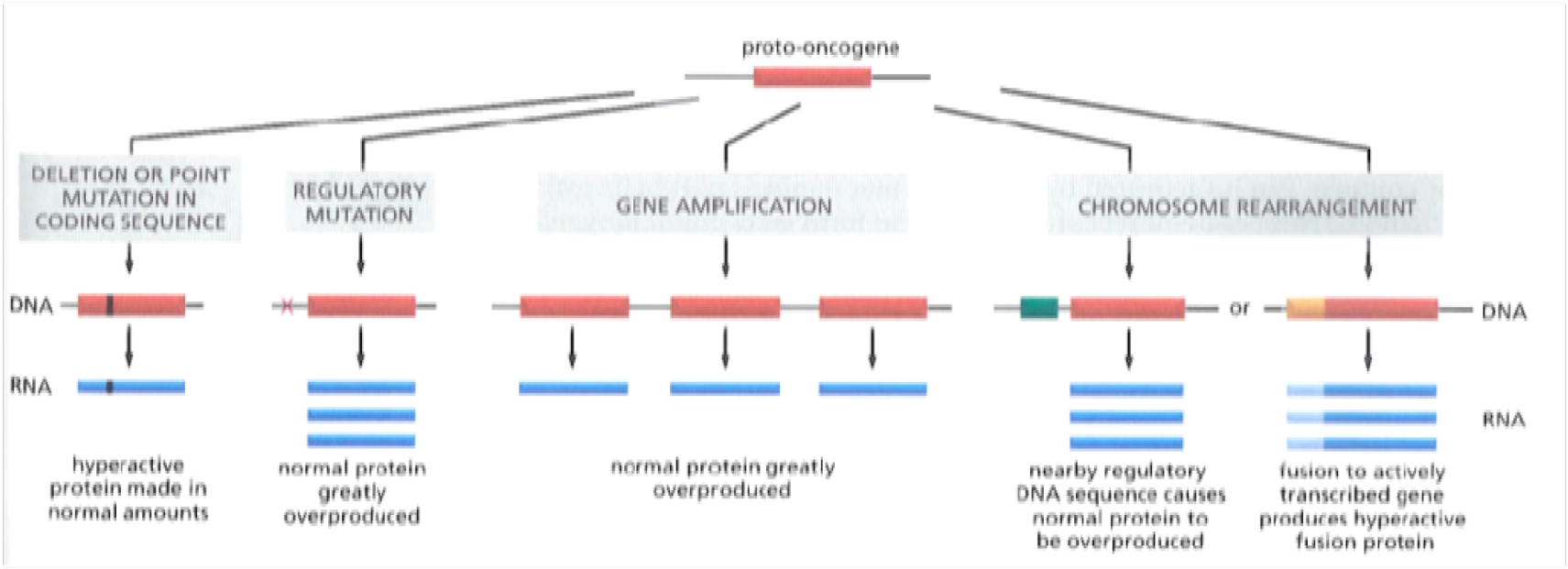
Cancer-Causing Genes

- Oncogenes
  - Mutations that confer gain of functions to oncogenes can promote cancer
  - Mutations with growth-promoting effects on the cell
  - Often heterozygous mutation is enough to make cells cancerous. Why?

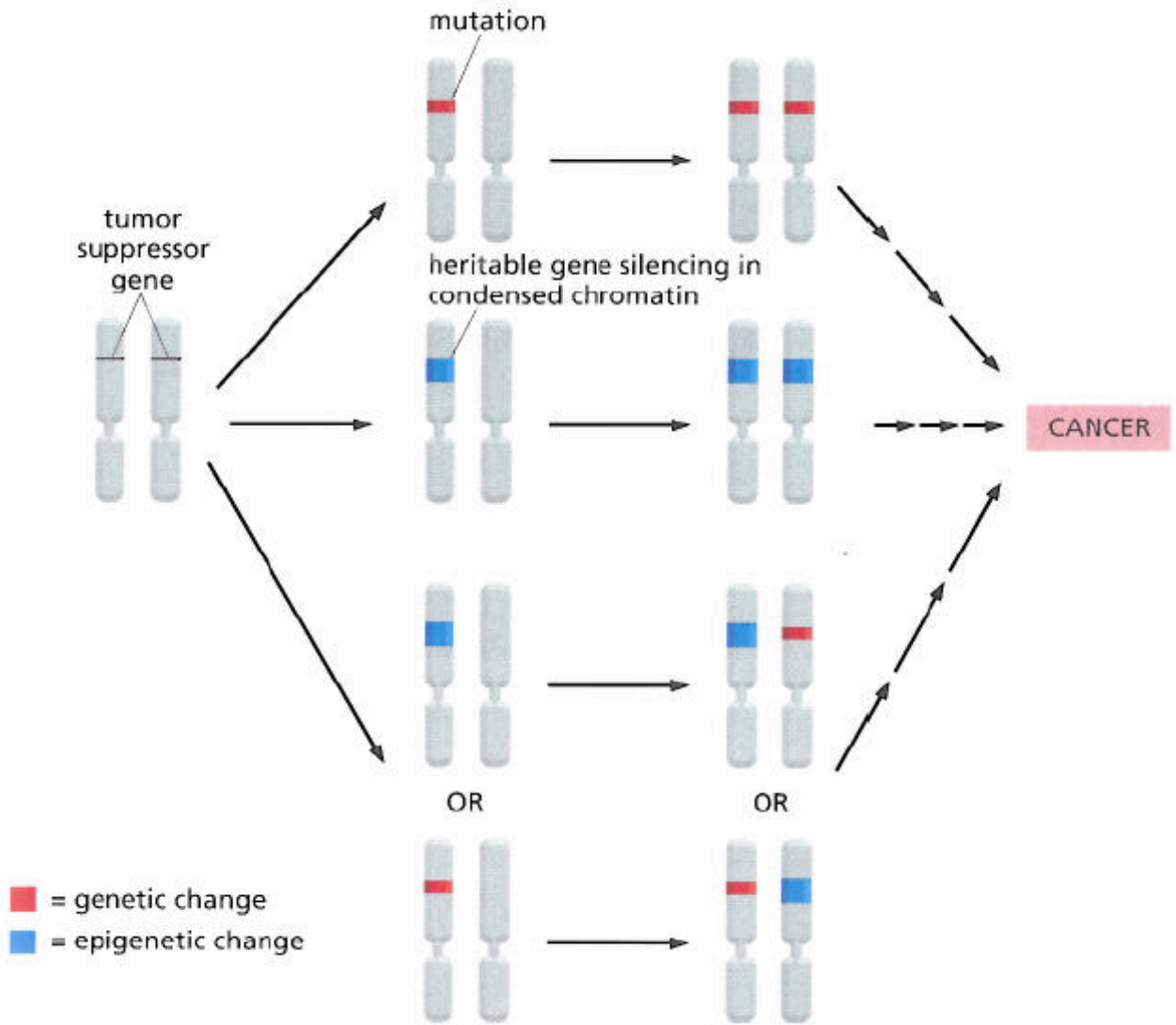
- Tumor suppressor genes
  - Mutations that confer loss of function to tumor suppressor genes can contribute to cancer
  - Typically homozygous mutation is required to make cells cancerous. Why?

- DNA maintenance genes
  - Indirect effects on cancer development

Mutations in Oncogenes



Mutations in Tumor Suppressor Genes



How to Find Cancer Causing Mutations

- Germline cancer mutations?
  - Genotype data are collected for a large number of normals and cancer patients (case/control studies)

- Somatic cancer mutations?
  - Genotype data are collected for blood (normal) and cancer cells for each cancer patient, for a large number of cancer patients.
  - What is the challenge?

Driver and Passenger Mutations

- Driver mutations
  - Causally implicated in oncogenesis
  - Gives growth advantage to cancer cells
    - E.g., mutations that de-activate tumor suppressor genes
  - positively selected in the microenvironment of the tissue

- Passenger mutations
  - Somatic mutations with no functional consequences
  - Does not give growth advantage to cancer cells
  - However, the passenger mutations are propagated to daughter cells just because they co-exist with the driver mutation in the same cell

- Key Scientific Question: How can we distinguish between driver and passenger mutations?

Identifying Driver Mutations

- Compare the tumor genome with the normal genome of the same individual
- Compare the tumor genome with reference genome
- Other known DNA polymorphisms
- Signatures of driver mutations
  - Frequently observed mutations across tumors
  - Mutations that characterize cancer subtypes
    - Mutations that cluster in subset of genes
    - Passenger mutations are more randomly distributed across genomes

Methods for Detecting Driver Mutations

- SIFT
  - A tool that predicts whether an amino acid substitution affects protein function
  - Classifies a substitution into tolerated or deleterious ones
- PolyPhen
  - Software for predicting damaging effects of nonsynonymous mutations

Overview

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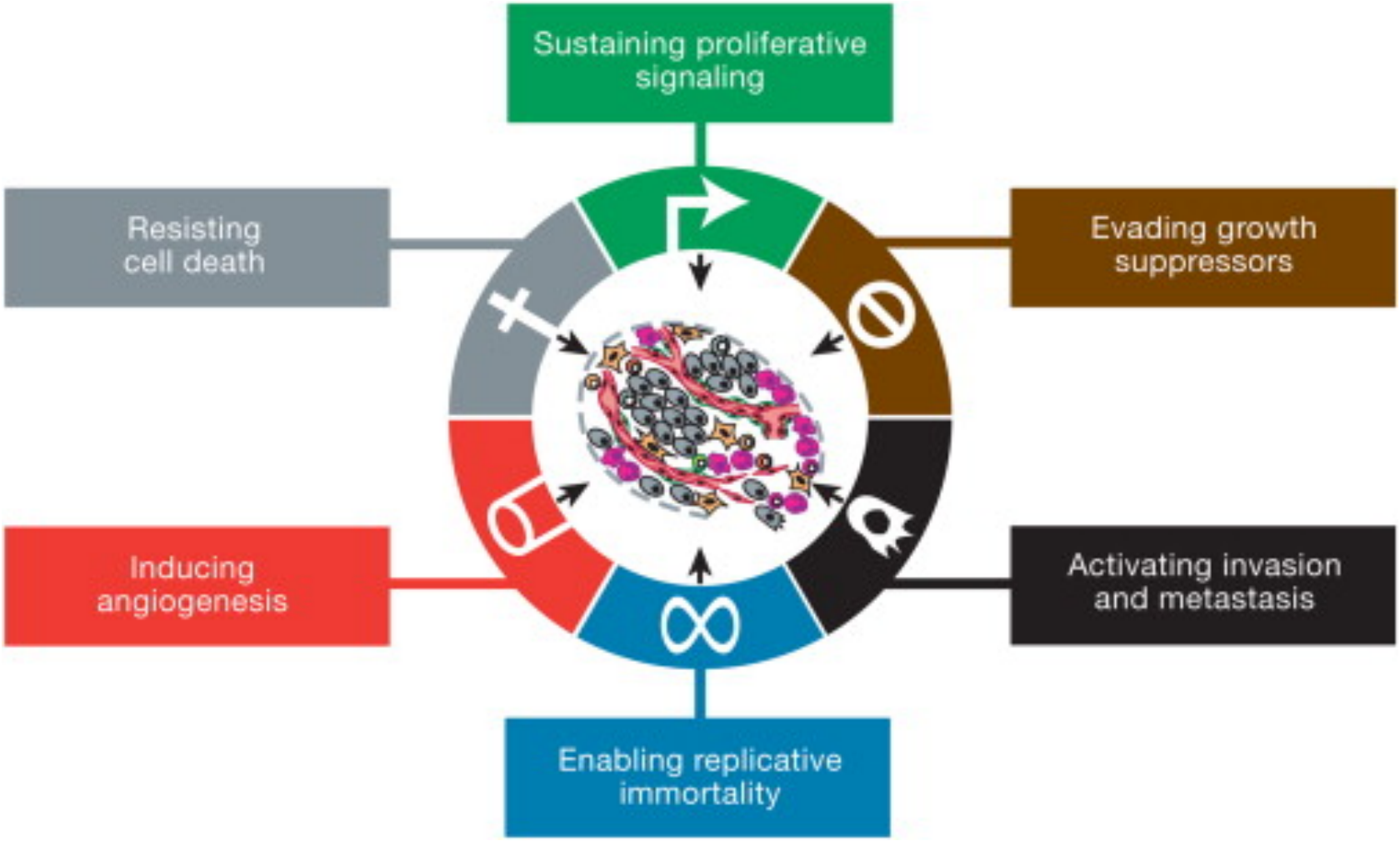
Why Do Cancers Sort Into Subtypes?



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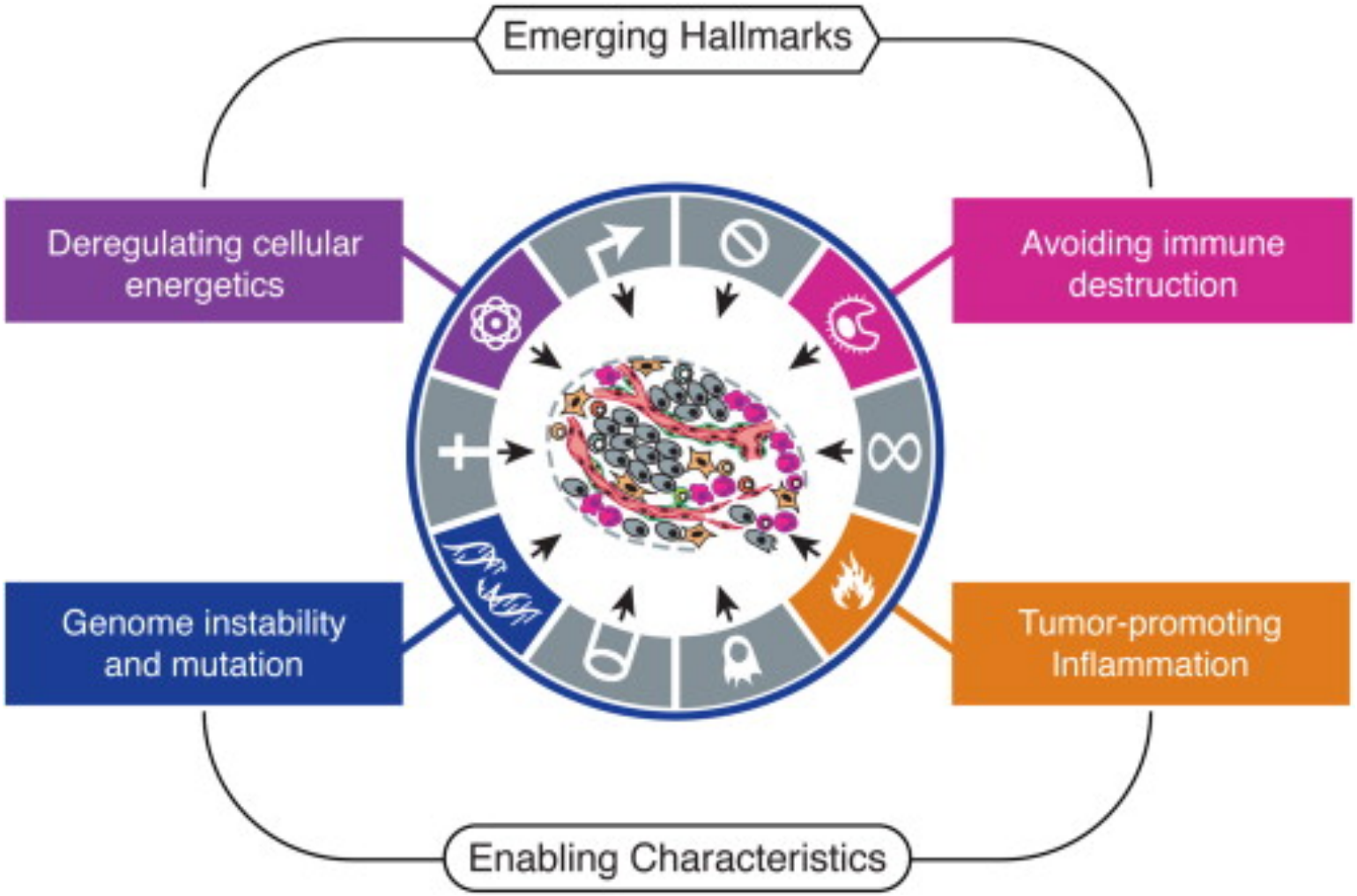
Why Do Cancers Sort Into Subtypes?



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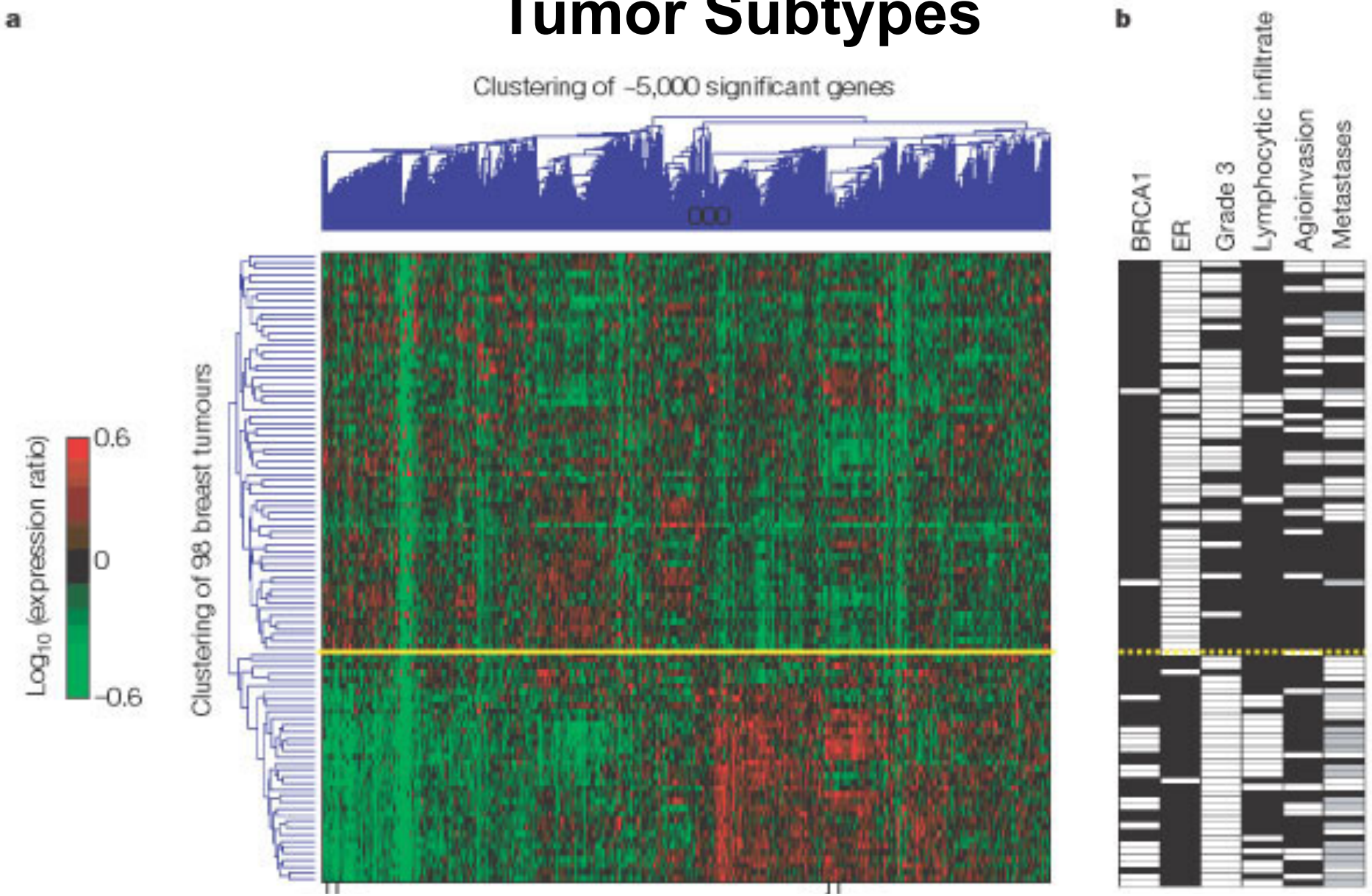
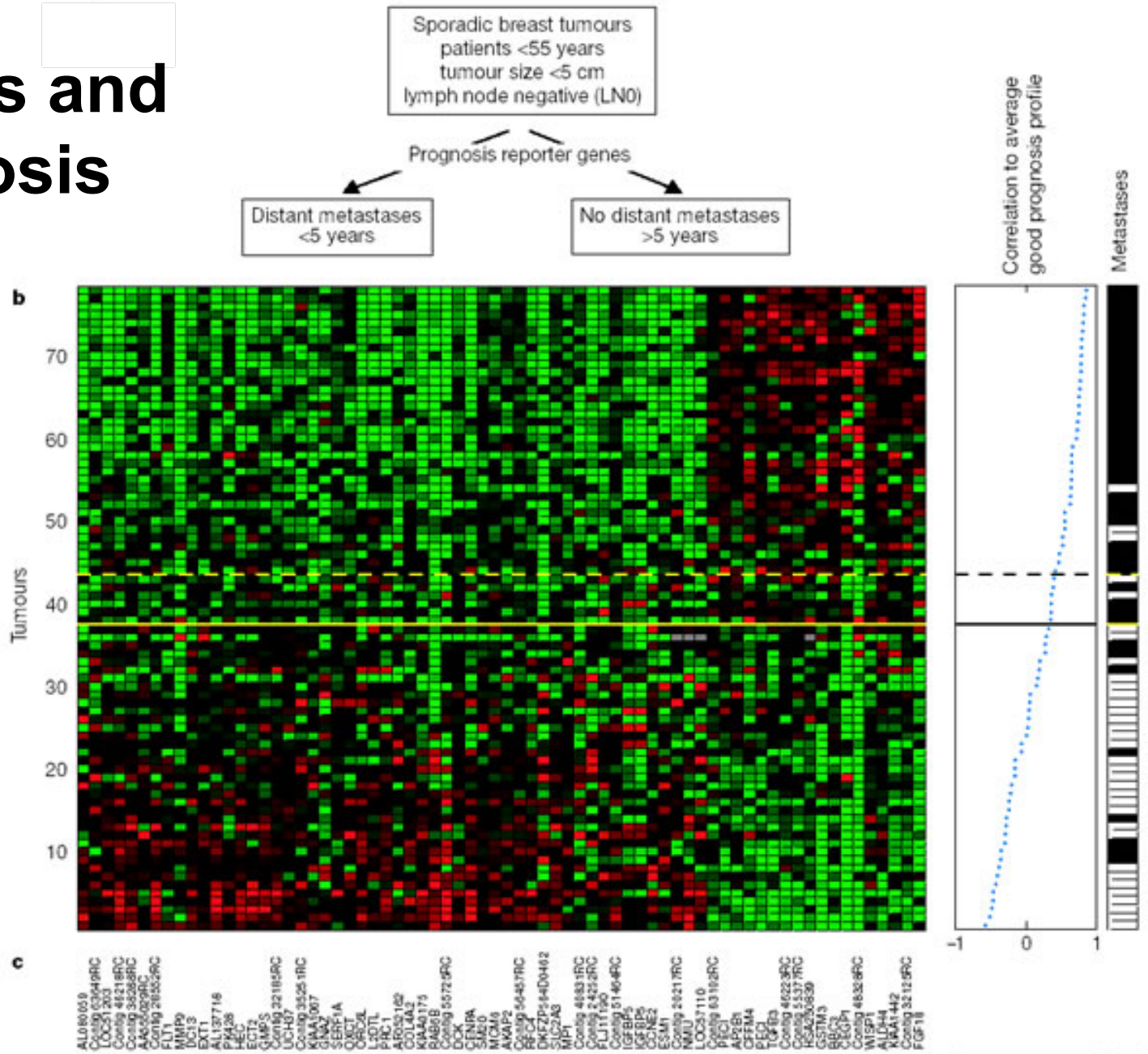
Tumor Subtypes



From: van't Veer et al., "Gene expression profiling predicts clinical outcome of breast cancer." Nature 415:530-536, 2001.

Subtypes and Prognosis



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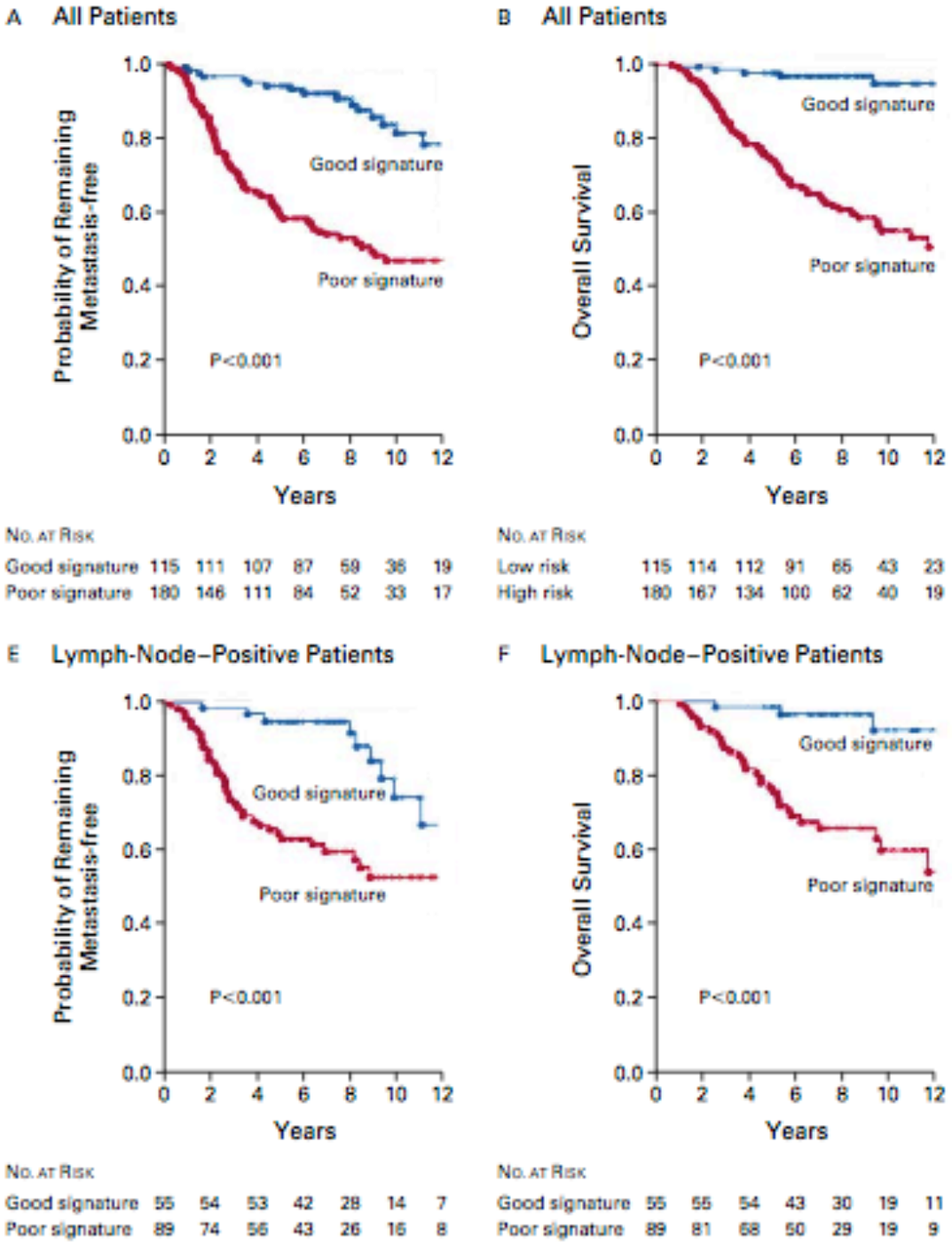
Genomic Diagnostics



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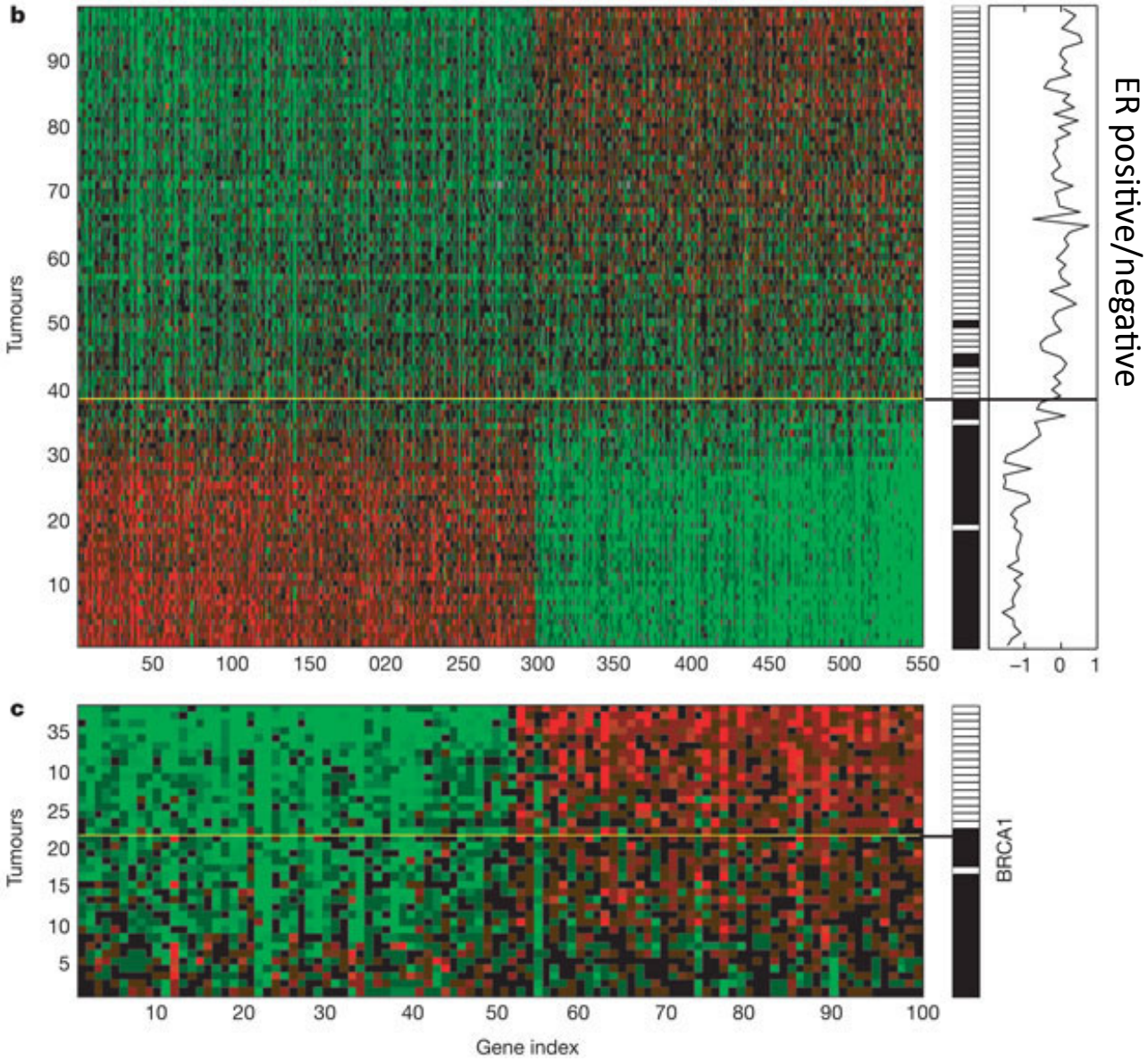
Expression Subtype Reflects the Genetic Basis of the Tumor



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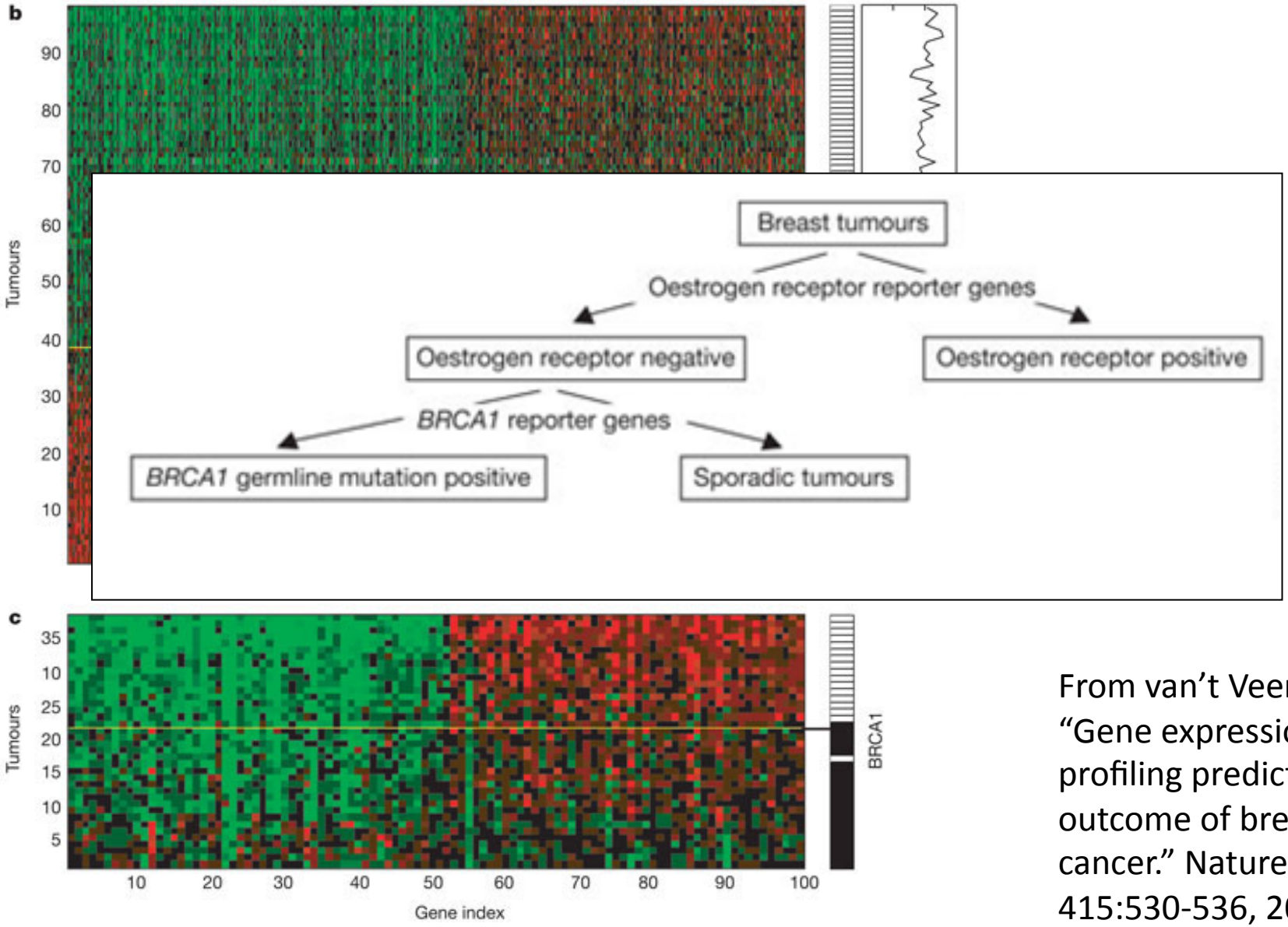

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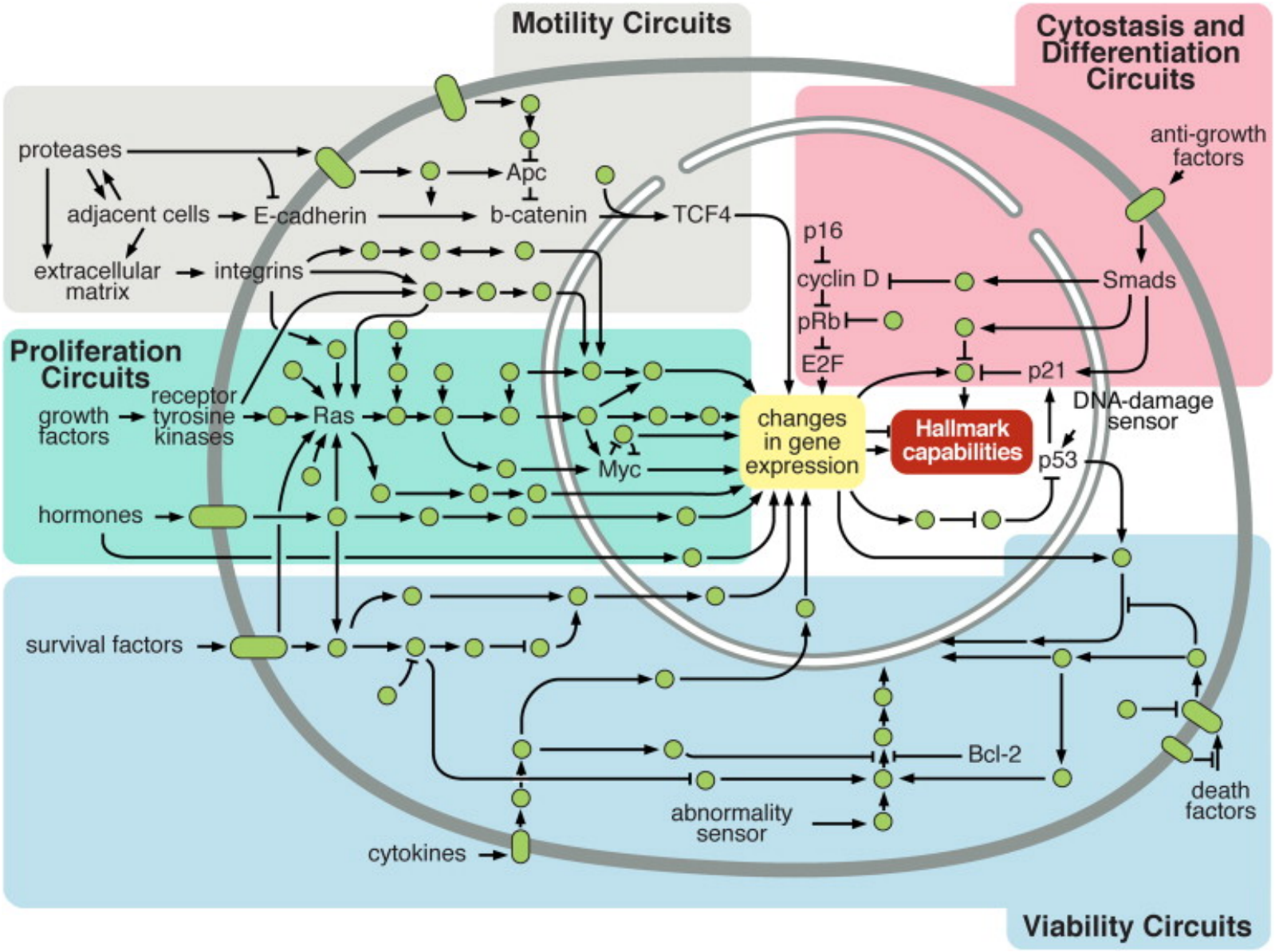
Interaction Networks Revisited



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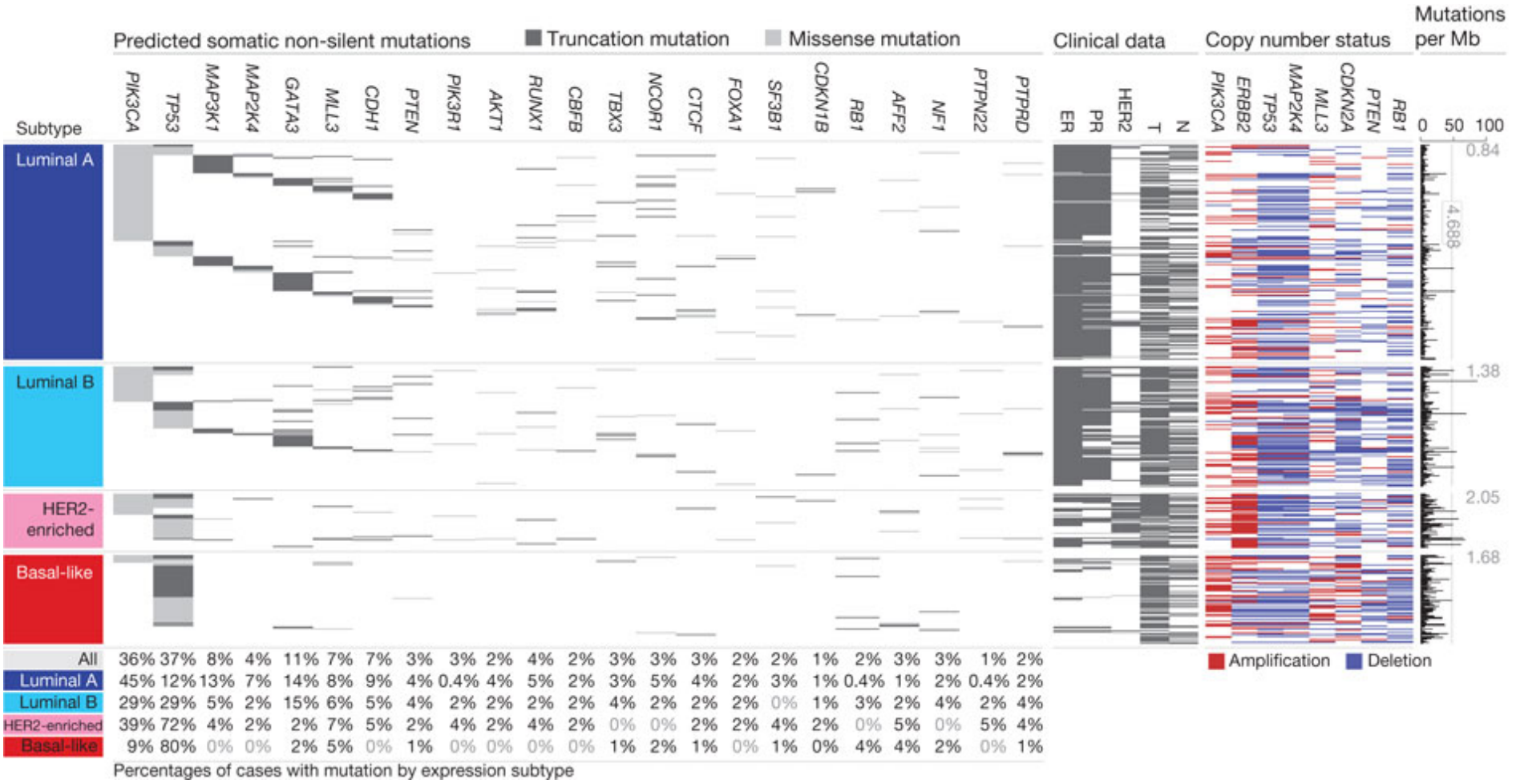
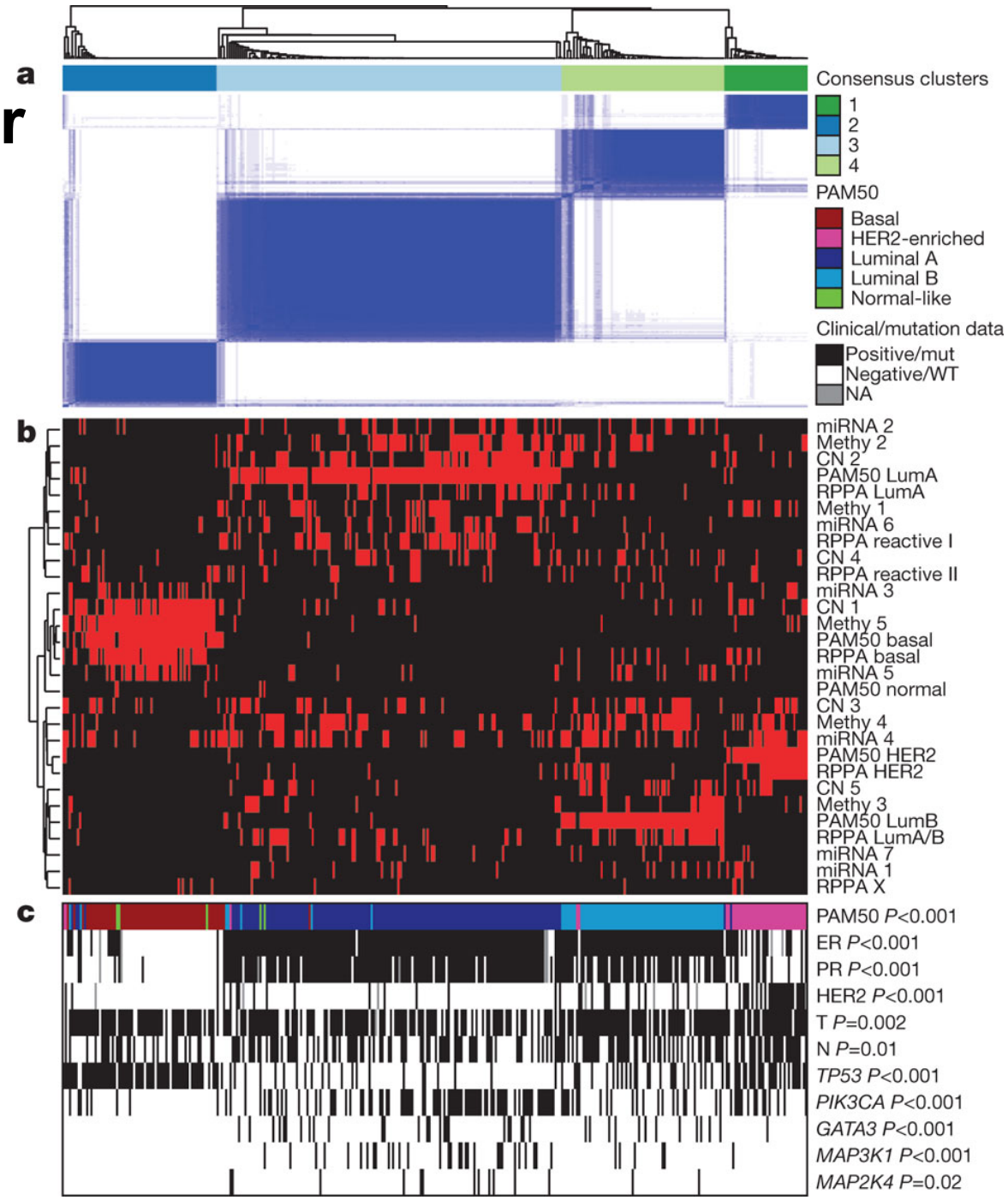
Example: TCGA Profiles of Breast Cancers



From: The Cancer Genome Atlas Network. “Comprehensive molecular portraits of human breast tumors.” Nature. 490:61-70, 2012.

Refining Tumor Subtypes



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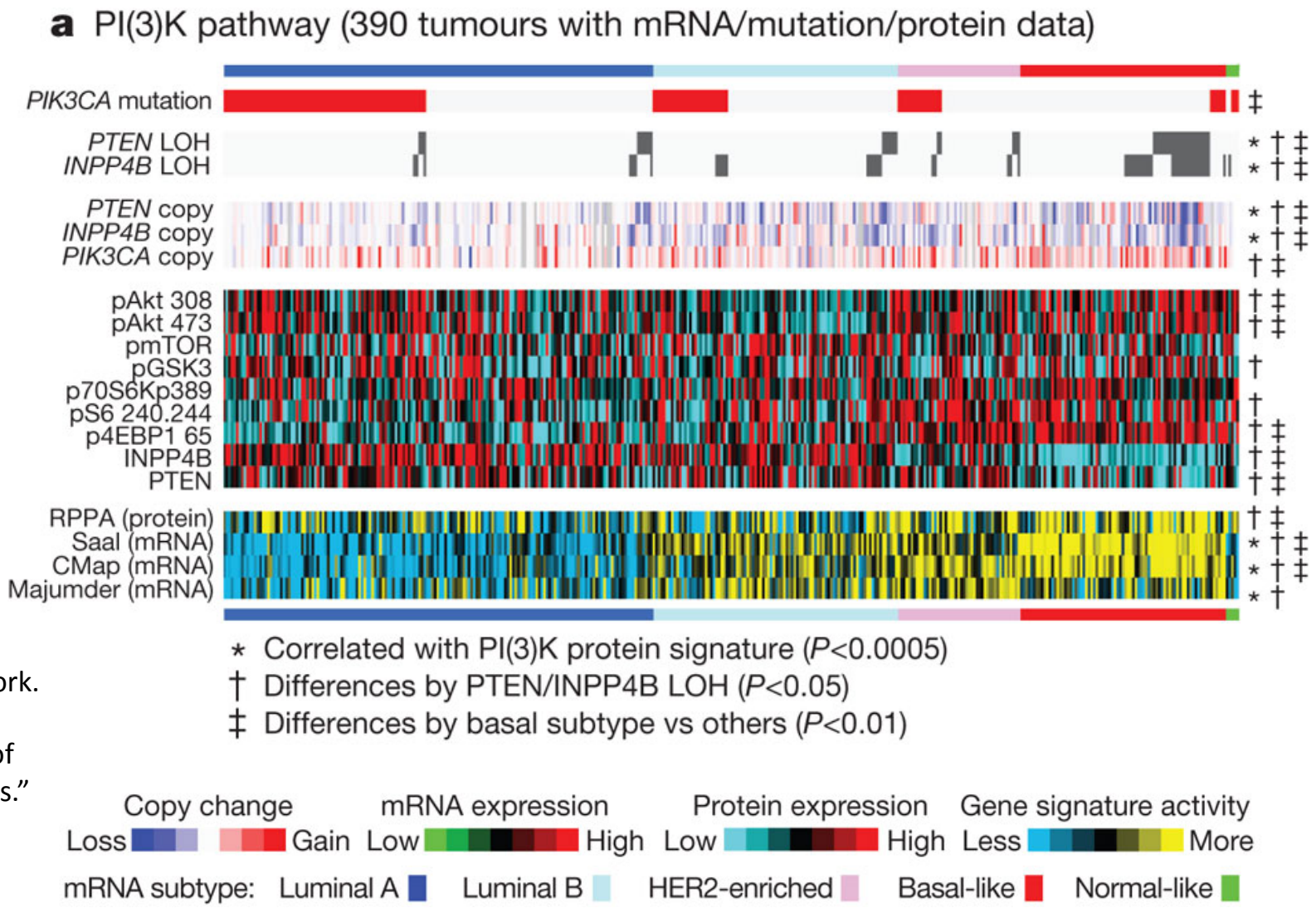
Diversities of Mutations Can Contribute to Common Functional Outcomes



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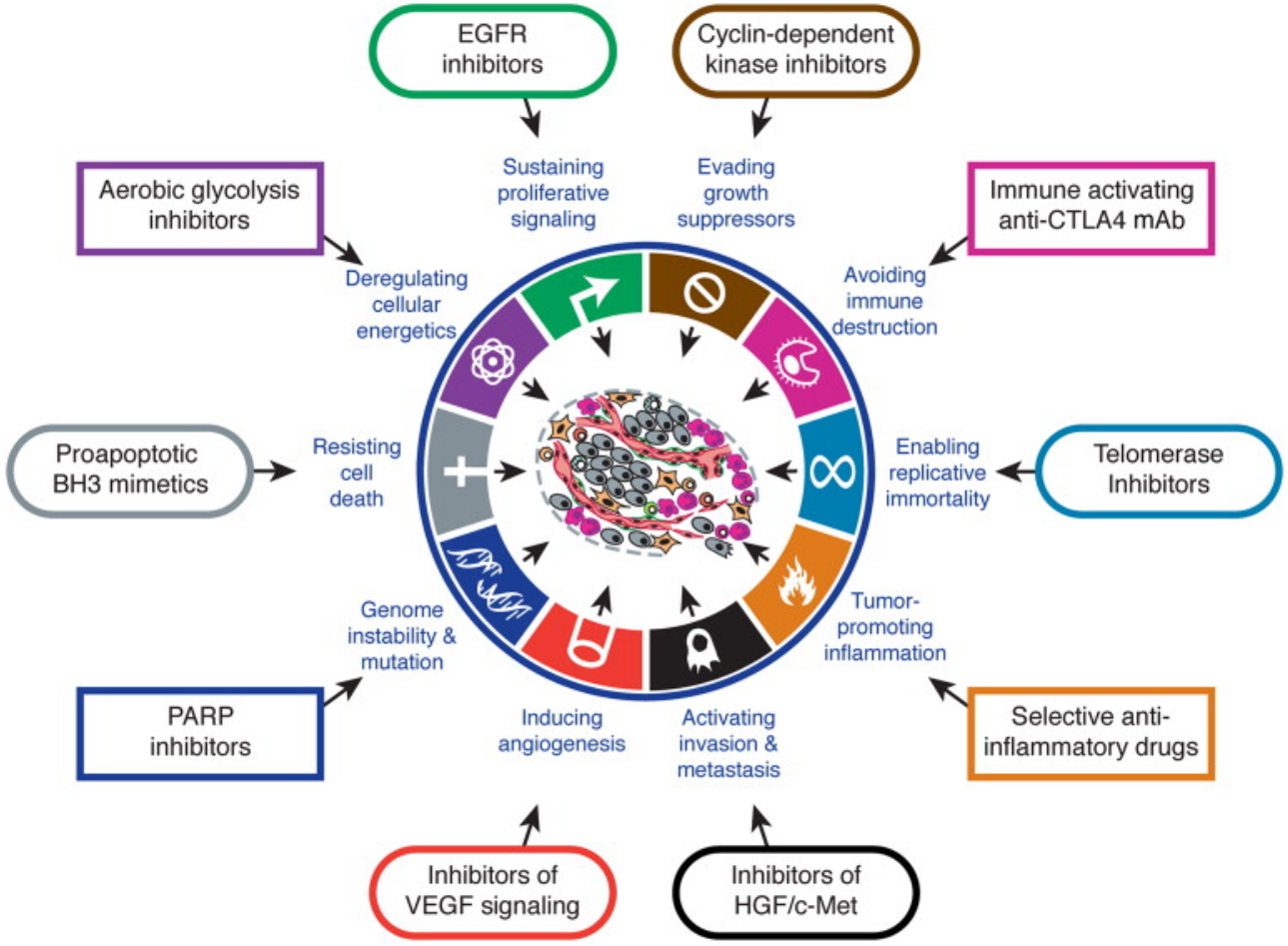
Understanding Cancer Genetics Help Us Develop New Therapies



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Genomic Signatures are Now Part of Cancer Diagnosis and Treatment

- Many expression signatures now available for different tumor types
- Often available as standard assays for cancer patients (e.g., Oncotype DX signature for breast cancers)
- Can help guide prognosis and treatment of cancers

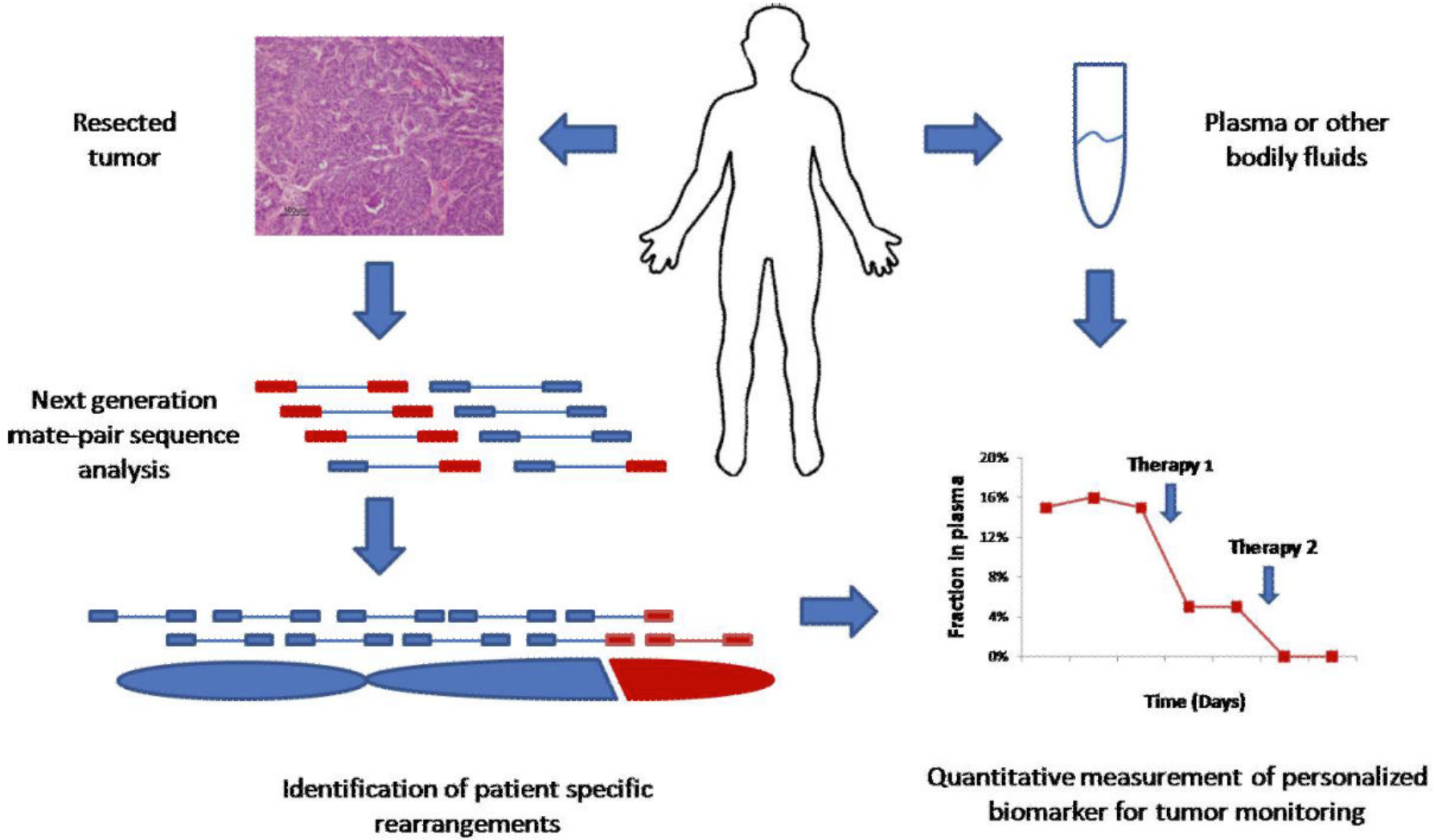
Examples of Targeted Therapeutics for Cancer

Therapeutic	Brand Name	Application
traztuzumab	Herceptin	Her-2 positive breast cancer
imatinib mesylate	Gleevec	chronic myelinoid leukemia, gastrointestinal stromal tumors
bevacizumab	Avastin	metastatic colorectal cancer, non-small cell lung cancer, Her-2 negative breast cancer
cetuximab	Erbitux	colorectal cancer
gefitinib	Iressa	non-small-cell lung cancer
erlotinib	Tarceva	non-small-cell lung cancer, pancreatic cancer

From Targeted Therapy to Personalized Therapy

- Many patients do not fit neatly into a subtype and there are many variations within each one
- Drugs that help for a subtype in general do not help every patient in that subtype
- Many subtypes probably not yet recognized or too rare to be selectively targeted
- Every tumor is, to some degree, unique at the genetic level

Bringing Personalized Therapy to Normal Treatment Practice



From: Leary et al. “Development of Personalized Tumor Biomarkers using Massively Parallel Sequencing.” Sci Transl Medicine. 2(20): 20ra14.

An Anecdote: Lukas Wartman

Diagnosed with lymphoblastic leukemia; after failing to respond to standard treatment, prognosis was hopeless .

Dr. Wartman happened to be a leukemia researcher; a team of colleagues decided to use him as a case study for personalized cancer treatment.

Genome/transcriptome completely sequenced and assembled in tumor and normal cells; computationally analyzed to find the specific cause of his cancer.

He turned out to have a strongly overexpressed gene: FLT3. FLT3 was not a known cause of leukemia, but it was a known cause of kidney cancer.

Dr. Wartman responded to a targeted therapeutic for FLT3-based kidney cancer and his cancer went into remission.

Reported in Kolata, “In Treatment for Leukemia, Glimpses of the Future.” New York Times, July 7, 2012.

Wartman's Experience is Not a Model for Most Patients (Yet)

- Sequencing still too slow and expensive for routine use
- Vast amounts of computing power required to process the data fast enough to put it in a usable form
- A team of experts needed to analyze and discuss the data to draw useful inferences from it
- But … sequencing is getting cheaper, computers are getting faster, and computational biology is getting better at automating these inferences

Overview

- What is cancer how does it develop?
- Genetics of cancer
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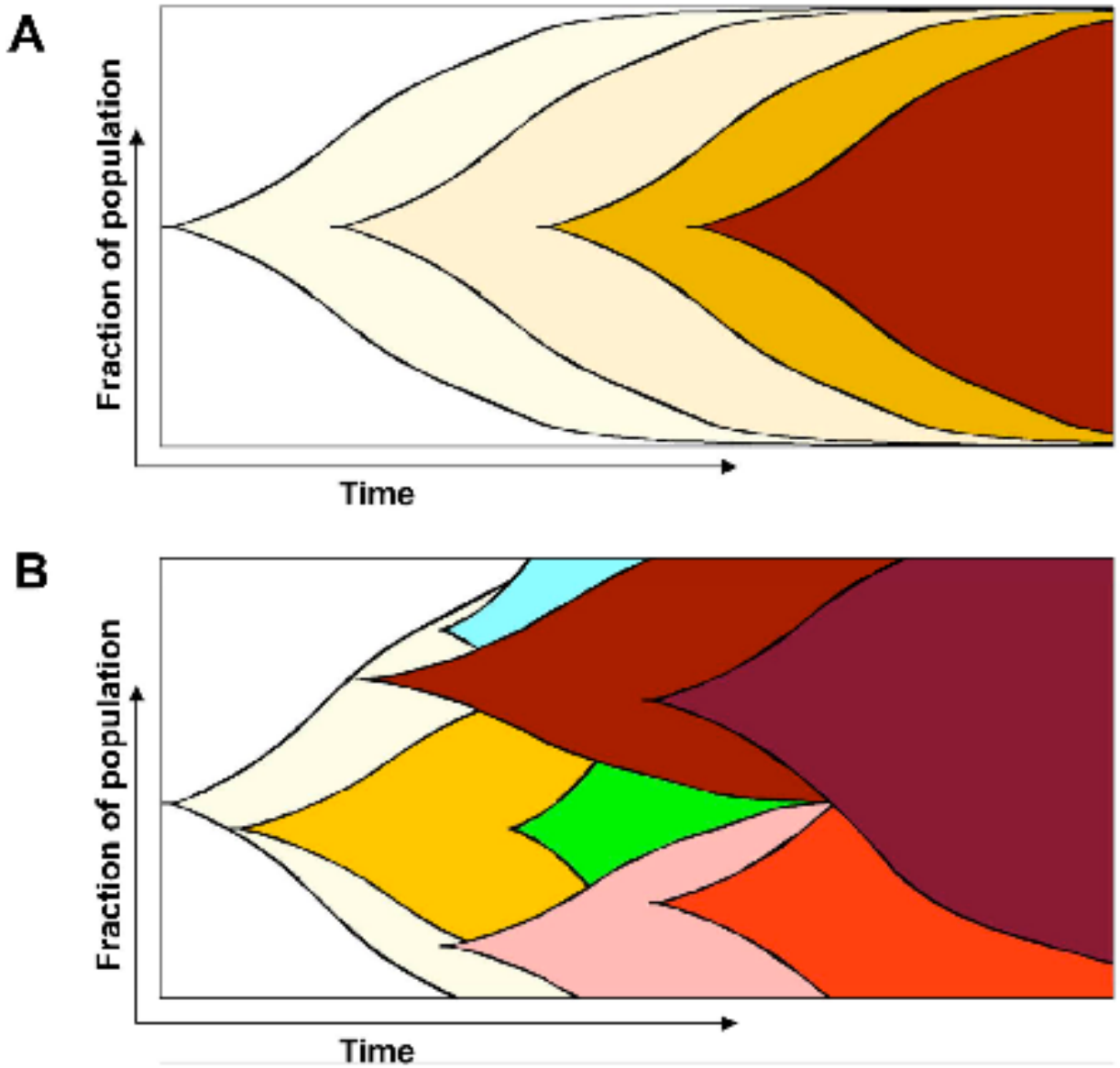
- Tumor heterogeneity

The Problem of Tumor Complexity

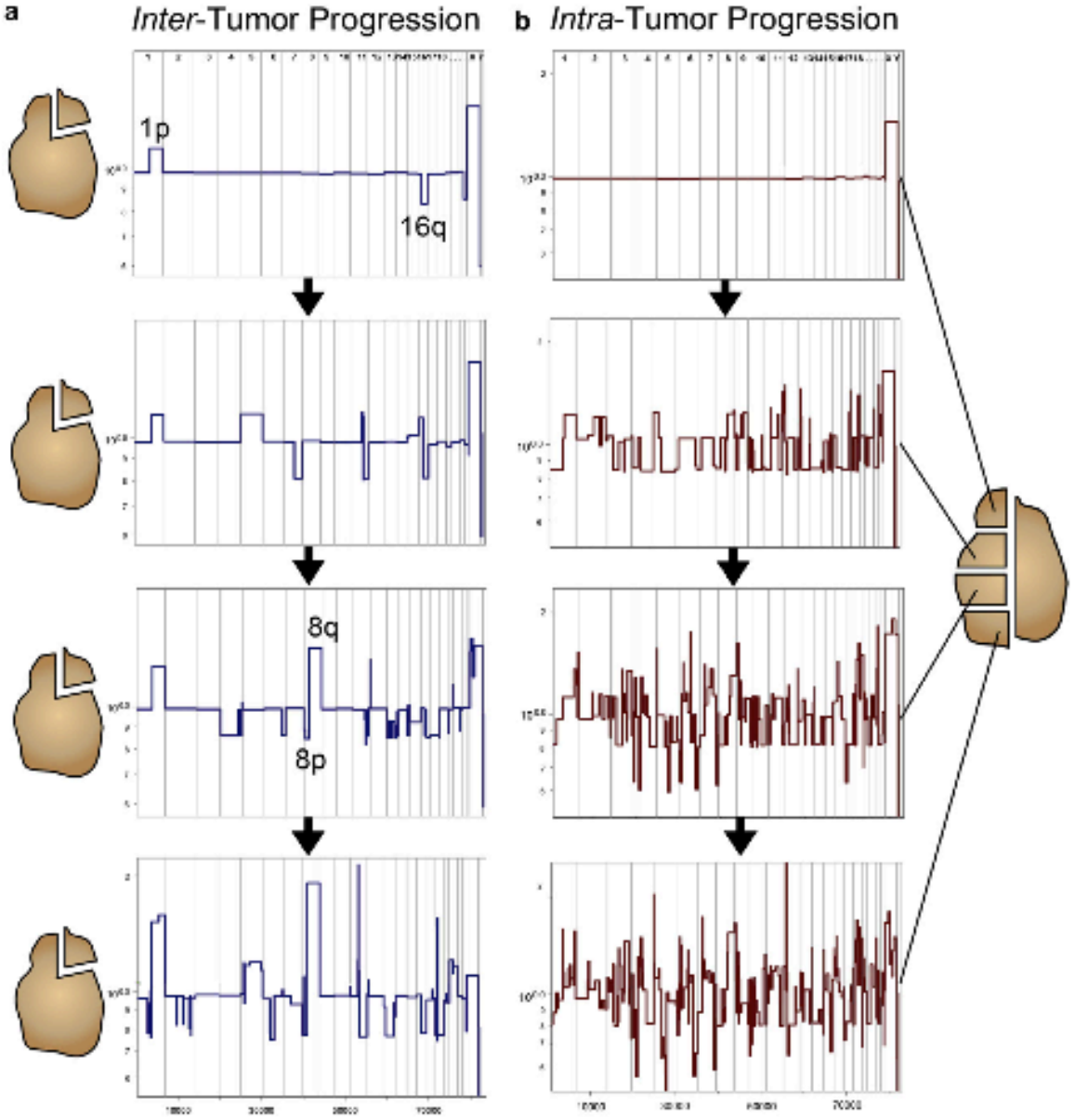
- The tumor genome varies from cell to cell: different cells have different combinations of mutations
- The tumor genome varies from day to day: tumors continue to evolve over time
- This has important implications for treatment: especially drug resistance

Why Does It Matter?: Heterogeneity and Evolution



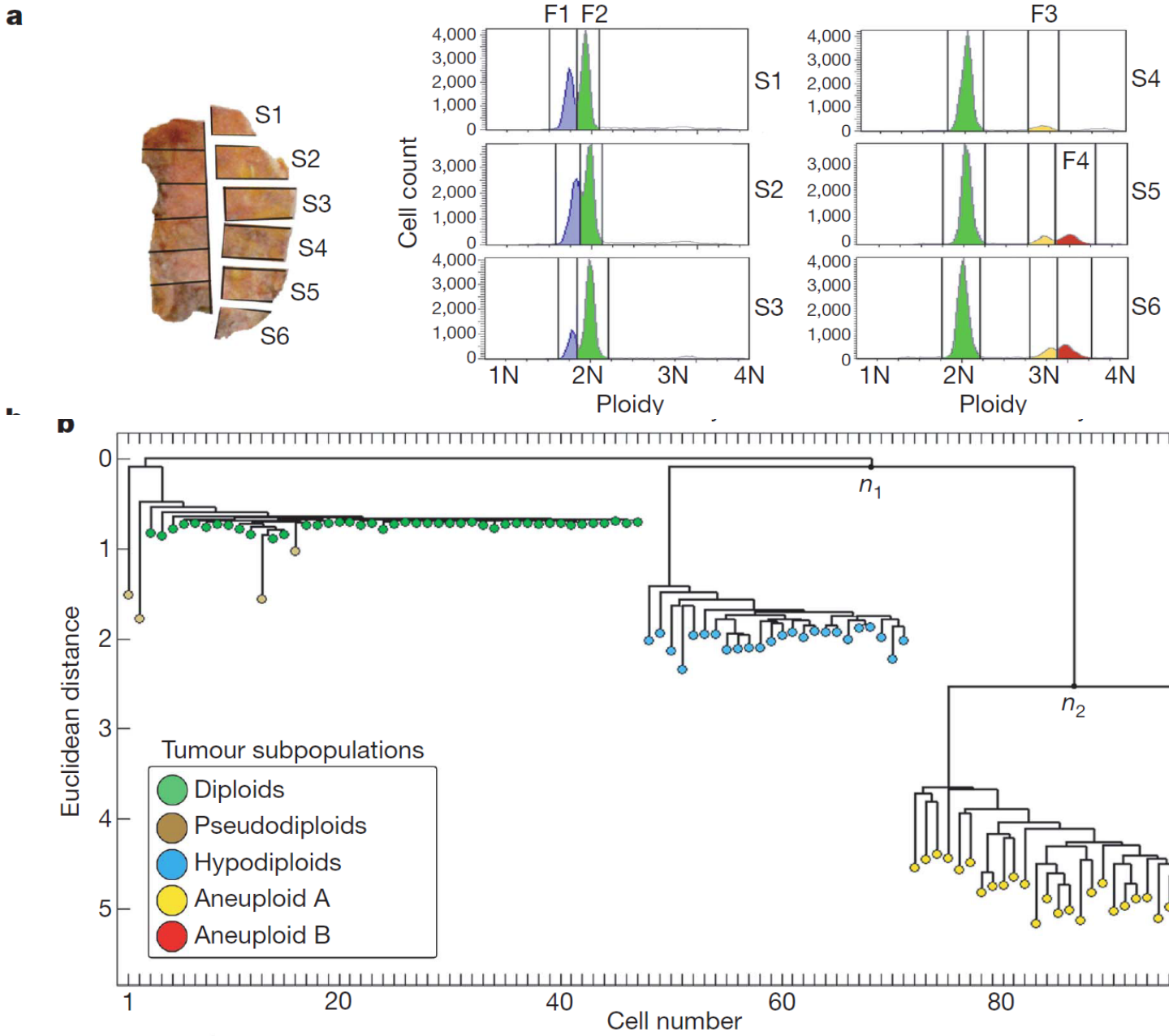
From: Marusyk and Polyak. "Tumor heterogeneity: Causes and consequences." Biochim Biophys Acta. 1805(1): 105, 2010.

Characterizing Intra-tumor Genomic Heterogeneity at the Single-Cell Level



From Navin et al. “Tumor evolution inferred by single-cell sequencing.” Nature. 472:90-94, 2011.

Tumor Phylogenetics



From Navin et al. "Tumor evolution inferred by single-cell sequencing." Nature. 472:90-94, 2011.

The State of the Art of Genomic Medicine for Cancer Therapy

The Good News

- Diagnostics and therapeutics based on tumor sub-types are now part of routine cancer treatment
- Many inherited mutations for tumor risk are known, some routinely used in treatment
- We have the knowledge to do much better for cancer treatment

The Bad News

- Truly personalized cancer treatment remains out of reach for most people; too costly and labor-intensive
- Tumor evolution is an unsolved problem; it is often only a matter of time before a tumor evolves to resist treatment

Challenges to Cancer Genome Analysis

- Somatic mutation calling is more challenging
  - the impurity of the sample
    - Normal genomes have allele copies of 0, 1, or 2
    - Cancer genomes can have allele copies of fractions of 0, 1, or 2
  - Most somatic mutations are rare

- Sequence alignment and assembly can be significantly more challenging because of highly rearranged chromosomes and high variation across cancer genomes

- Different cancer types have different rates of mutations. Mutator phenotype may or may not present.

- Infrequently occurring driver mutations are hard to identify.

Summary

- The genetic causes of cancer include both heritable germline mutations and somatic mutations
- The key challenge in studying the genetic causes of cancer is to identify driver mutations from background passenger mutations
- From cancer genomic data, we can learn subtype information that can be used for personalized therapy
- Tumor heterogeneity can be examined from single-cell sequencing